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Upscaling Mechanochemistry: Challenges and Opportunities for Sustainable Industry

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Abstract

Mechanochemistry provides an environmentally sustainable approach to prepare and process molecules and materials and offers a new research space full of opportunities. However, its full industrial potential has not yet been realized. Herein, we discuss opportunities offered and challenges laying ahead for the adoption of mechanochemical manufacturing technologies into industry.

Keywords: Mechanochemistry; Upscaling; Innovation; Green Chemistry; Reactive Extrusion; Ball milling.

Traditionally, solution-based processes have dominated laboratory set-ups and industrial manufacturing protocols since modern chemistry was established and the first chemicals were manufactured at large-scale in the early 17th century. From alchemy to chemistry, the mortar and pestle is considered to be the first established piece of chemical equipment and was used in the earliest written record of a mechanochemical reaction in 315 BC. However, overshadowed by solution chemistry throughout history, it was only in the late 19th century when it was considered to be of equal standing to thermochemistry, electrochemistry, photochemistry, and other types of synthetic methodologies [1].

However, despite being under the shadows for centuries, the use of mechanochemical techniques in chemical synthesis has experienced a vigorous revival over the past few decades. Nowadays, the humble mortar and pestle has given way to automated mechanochemical equipment (Figure 1a), which allowed a plethora of chemical transformations in a wide range of chemical fields (*e.g.*, organic, inorganic, materials). Notably, the once-obscure field of mechanochemistry has taken the synthetic chemistry spotlight as it provides a means of avoiding potentially harmful organic solvents, whilst reducing reaction times. Furthermore, within this new chemical space, new opportunities can be explored (*e.g.*, insoluble precursors), leading to different reactivity patterns and enabling preparation of inaccessible products. Importantly, its complementary nature to traditional solution-based methods opens-up new chemical perspectives and challenges in the chemical sciences [2].

The global need for cleaner and more sustainable chemical transformations to achieve the United Nations Goals for Sustainable Development (SDGs), together with the 12 principles of green chemistry [3] and engineering [4] (Box 1), have propelled mechanochemistry from a mere curiosity to being named by IUPAC as one of the ten innovations in chemistry that will change the world [5]. These advancements are supported by the recent creation of dedicated research centers (*e.g.*, NSF Center for the Mechanical Control of Chemistry (CMCC), 2020) in addition to historical ones (*e.g.,* Russian Institute of Solid State Chemistry and Mechanochemistry, 1997); as well as the creation of collaborative networks of scientists and technologists, funded by intergovernmental funding agencies (*i.e.*, European Programme COST Action CA18112 – MechSustInd), which complement historical organisations associated with the International Union of Pure and Applied Chemistry (IUPAC) (*e.g.,* the International Mechanochemical Association – IMA, 1988).

Researchers responded to this reawakening by pushing the boundaries of mechanochemical synthesis, and scaling-up mechanochemical processes. In terms of scaling-up for large- or industrial-scale implementation, a common misconception is the need for physically larger reactors and ancillary equipment. While this perception has valid roots stemming from a traditional batch processing mindset (from small flasks in a teaching or research laboratory to large industrial vessels), it does not hold true when continuous processes are considered.

Performing large-scale reactions neat or comprising of minimal solvent (or co-solvent), is not uncommon, particularly when employing continuous/flow systems, where reactive solutions are pumped through tubular or micro- reactors [6]. However, matters get increasingly complicated when one (or all) of the reagents, are solids. Their controlled reaction is nontrivial, especially in a continuous fashion, where solids need to travel a certain distance, meet, react, and continue their journey to the next unit operation (Figure 1b).

Batch processing has been mainly scaled-up using planetary ball mills, with successful chemical transformations including the synthesis of drug and fungicide precursors, as well as metal complexes and catalysts [7]. Larger scales have been successfully implemented in several fields (metallurgy, biomass treatment, energy materials, *etc.*) using eccentric vibrating mills and Simoloyer set-ups. In addition, researchers have relentlessly investigated and rationalized the effect of mechanochemical parameters (*i.e.*, powder-to-ball ratio, free volume present and movement of ball bearings, *inter alia*) on chemical reactivity, as well as mechanistic studies – which is crucial for the future expansion of the mechanochemical field [8-9].

When considering ball-milling batch processing methodologies, two drawbacks arise, *i)* scalability and *ii)* temperature control. With exception to bespoke compounds, ball milling neither satisfies the required economically feasible production rates nor can the temperature be precisely controlled. Noteworthy, despite the technology being customized by several researchers to allow temperature control in ball-milling systems, there are no commercially available variable temperature systems.

An alternative technology, allowing simultaneous continuous processing and temperature control, is twin screw extrusion (TSE) (Figure 1a). TSE allows for a considerable range of throughput rates to be achieved, whilst maintaining a constant equipment footprint, confirming further that a scale-up in equipment size is not necessary. Furthermore, continuous solid dosing, reactive extrusion, co-crystallisation or granulation processes are readily performed in various industries, including regulated environments such as the food and pharmaceutical industries, whilst providing accurate temperature control (to 2 d.p.). As a result, more fundamental questions need to be asked: *What is so different about mechanochemistry? What does it mean to scale-up a mechanochemical process? Why should we scale the process up?* and *How can we do it?* (Figure 1c)

Mechanochemical synthesis by TSE is now a vibrant and rapidly evolving field of research, with a substantial library of successful chemical transformations associated with it. This has led to an increasing number of research groups and start-up companies beginning to exploit and capitalize on this technology. Moreover, TSE allows for the combining of several synthetic steps into one process, which is of pinnacle importance, since most commercial compounds require complex multi-step synthesis, typically carried out as subsequent batch processes (Figure 1b). Indeed, multi-component reactions and multi-step processes (*e.g.*, coupling of an Aldol and Michael addition) have been successfully conducted as a one-step, large scale, continuous process, *via* TSE [10].

Mechanochemistry has the potential of becoming an extreme form of process intensification, where processes are carried out under solventless or minimal solvent conditions, with extremely competitive *E*-factors for otherwise complex transformations. While process intensification is undoubtedly a success factor at process development stages, the lack of literature showcasing large-scale (>100 mmol) synthetic mechanochemistry remains an enormous obstacle [11,12]. Without sufficient examples of extensive scale processes independently reported by researchers worldwide, there is a risk of perpetuating the label for mechanochemistry as a mere academic curiosity.

Research and Development (R&D) pilot and large-scale experiments are expensive, require appropriate infrastructure, and highly trained personnel, which limits the number of publicly funded research groups able to generate the experimental evidence required to show that the technology is ready to perform at the next level. In innovation and R&D management, the pilot-scale stage is known as "*the valley of death*", given the combined effect of uncertainty of success, rising costs and unclear market demand [13]. Moreover, high pressure to get to market fast leads to short time given to develop a robust process. Under the circumstances, a natural tendency is to rely on familiar and well tested technologies, leading to a vicious circle.

However, a way to bridge this gap, in the short term, would be channeling research efforts on synthetic mechanochemical transformations for manufacturing low-volume-high-value chemicals such as commercial ligands, catalysts and/or potent drugs (Figure 1d) [14].

By targeting compounds that only require hundreds of kilograms a year to be manufactured, the research community will gain confidence towards mechanochemistry and increase the number of successful business cases. This will challenge the current negative perceptions on upscale and start attracting industrial attention towards an area that has already shown greener and more efficient processes at laboratory scales.

Imaginably, future process scientists and technologists will not only discuss batch *vs.* continuous, but solution-based *vs.* mechanochemistry, and ball milling *vs.* TSE (Figures 1c,d). This will promote behavioral changes towards green and energy-efficient manufacturing processes, fostering productivity at lower costs and gaining expertise in quality, safety, and competitiveness in the chemical industry.

In addition to scientific and technical aspects, development of existing sustainability laws and implementation of social and economically responsible financial and governmental policies would boost appropriate public and private investments, required for industrial retooling or to retrofit existing infrastructure. Moreover, significant changes in education (*via* the acquisition of new skills, the introduction of program accreditation policies or by linking curricula to real-world case studies in green technological innovation) and environment-to-economy-model relationships are necessary to accelerate new long-term growth strategies, as well as to engage the private sector (Figure 1e).

Moreover, incentive mechanisms will have to be enhanced to reward pioneering efforts and early adopters of mechanochemical techniques. This could be implemented *via* innovation agencies, pertinent stakeholders (*e.g.*, philanthropic funders and chemical societies), more Awards and Prizes (*e.g.*, European Union Innovation Radar Prize and the Green Chemistry Challenge Awards), aiming to identify cutting-edge innovations and new chemistry processes. Products and technologies that have the potential to impact society, business, public health, and the environment should be recognized internationally.

Overall, future systemic structural and political changes, together with educational and end-user behavioral changes could drive companies to adopt socially responsible norms and initiatives for sustainable continuous manufacturing, even if not yet legally required. This will not only increase their reputation and socially (eco)-conscious image, but also create the synergy required for a global sustainable mindset change.

In summary, we hope we have highlighted challenges and opportunities offered by a broader adoption of mechanochemistry at medium to large-scales for chemical manufacturing. While we do not propose mechanochemistry to fully replace existing solution-based methods, this underutilized alternative should be given a better chance to demonstrate its benefits in manufacturing. To overcome the challenges surrounding its industrial adoption, final users, basic scientists, engineers, the public and private industrial and educational sectors, as well as funding agencies have to synergize on the common vision of “sustainable advanced manufacturing”. We envisage that the seminal translation of upscaled mechanochemical methods into commercial processes, starting with low-volume-high-value chemicals will generate the right industrial traction that ultimately will transform how chemicals will be produced in the future.

Conflicts of interest

There are no conflicts of interest to declare.

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Resources

i ACS Green Chemistry Institute – Design Principles for Sustainable Green Chemistry & Engineering. https://www.acs.org/content/acs/en/greenchemistry/principles.html , accessed February 1, 2021.

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Box 1. Design Principles of Green and Sustainable Chemistry and Engineering.

Over the past decade, there has been a renaissance in solid-state mechanochemical routes to chemicals and materials, driven by the need for greener manufacturing technologies. Mechanochemistry not only offers a straightforward approach to the "*12 Principles of Green Chemistry*" (Figure I), but offers a new chemical space for making and screening novel molecules and materials.

However, not only these principles have to be considered when attempting up-scaling and industrial implementation of mechanochemical techniques – this task is paved with technical and engineering challenges. The discipline of engineering, *via* "*12 Principles of Green Engineering*" (Figure I) has also mapped their foundation towards more sustainable industrial manufacturing processes.

Upscaling mechanochemistry to industrially meaningful scales will only be achieved when these two disciplines create the synergy required to solve the many challenge ahead – which are not immiscible isolated chemical or engineering difficulties but an 'azeotropic" mixture of both. Hence, for mechanochemistry to fulfill its disruptive industrial potential, chemistry and engineering have to be considered as a single intimately intertwined discipline with the common goal of making the world more sustainable.

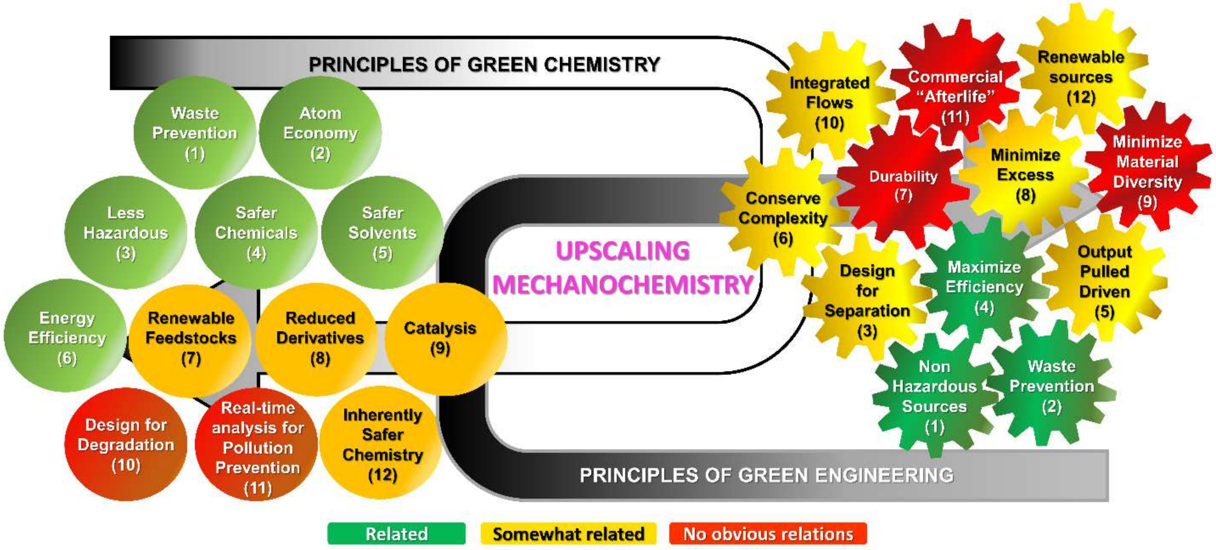

Figure I, Green Chemistry and Engineering principles[i] classified in relation to their connection to upscaling mechanochemistry.

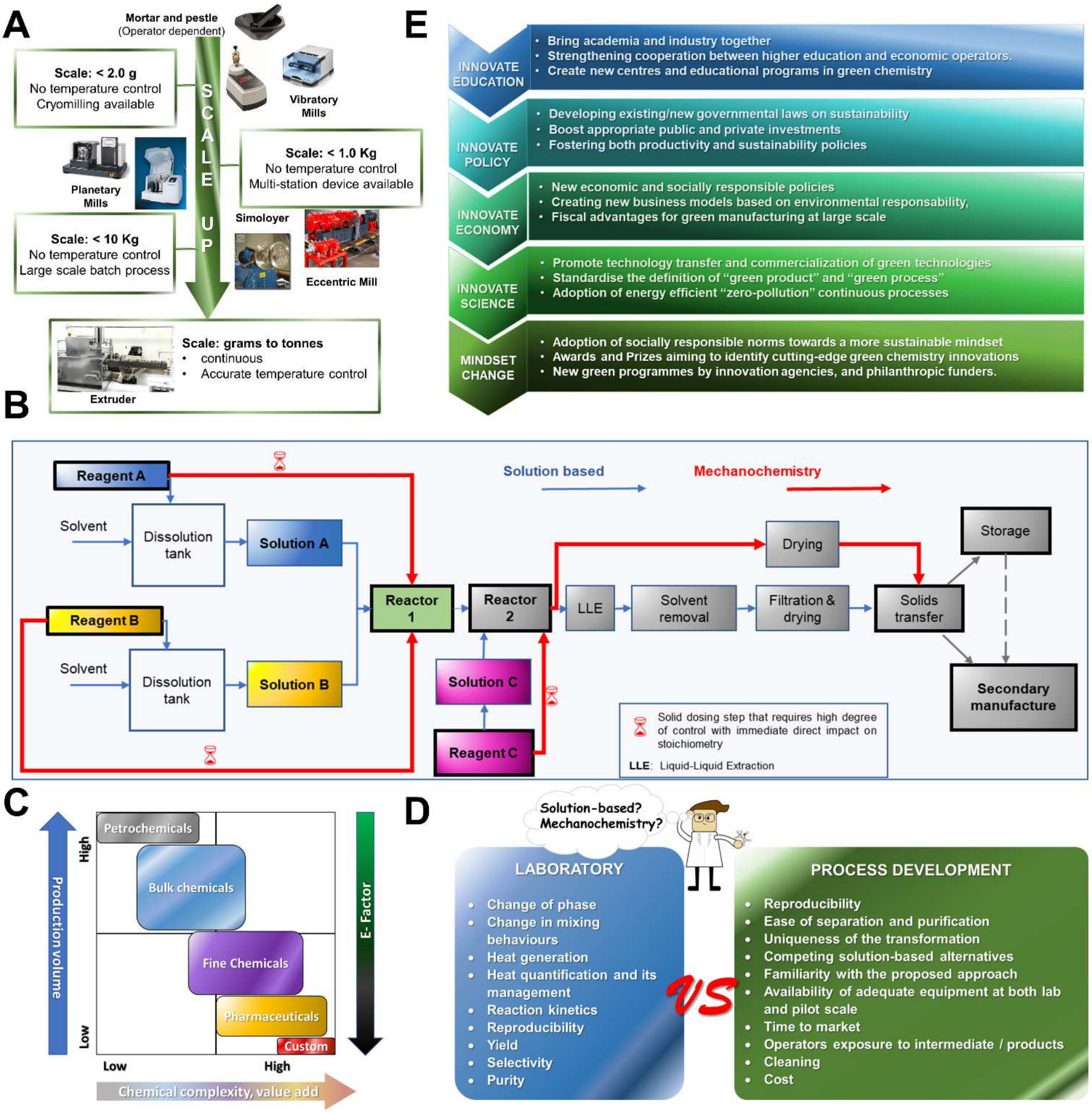

Figure 1. Instrumentation, processes, and parameter influencing the upscaling of mechanochemistry. (A) Schematic illustration of mechanochemical scaling (from a mortar to TSE). Images reproduced with permission. (B) Differential workflow for a large scale three component reaction (*A+B+C --> Products*) under conventional solvent-based methodologies (blue arrows) and solvent-free mechanochemical conditions (red arrows), (C) Mechanochemical upscaling spectrum (Volume *vs* value add *vs* E-factor), (D) Factors and consideration affecting laboratory scale synthesis (left) and large-scale process development (right), and (E) Drivers for the change towards the sustainable

continuous manufacturing by mechanochemistry. For further ‘drivers for change” examples see www.beyondbenign.org.